REMARKS

Overview

Claims 1-4, 34-74, 85 and 99 are examined on the merits. Claims 75-84 and 86-98 have been canceled. Claims 1-65, 67-74, 85 and 99 have been amended. Claims 100 and 101 have been added. Support for these amendments and new claims may be found throughout the published specification, for example, at paragraphs 9, 143, 202-203, Figure 2 and Table 1. No new matter has been added.

Applicants gratefully acknowledge the withdrawal of the rejection of claims 2 and 85 under 35 U.S.C. § 102(b) by LaTemple. Applicants thank Examiner Holleran for the courtesy extended during the telephonic interview held August 27th during which the claims, rejections and cited references were discussed but no agreement was reached with respect to the claims.

The present response is an earnest effort to place all claims in proper form for immediate allowance. Reconsideration and passage to issuance is therefore respectfully requested.

Claim Rejections Under 35 U.S.C. § 112

A. Claims 34-65 and 68-74 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states the claims are drawn to specific named species of cell lines and that the rejection would be obviated by amending the claims with product-by-process language so that the claims were generic and did not recite a specific, named cell.

Applicants thank the Examiner for this suggestion and accordingly have amended claims 34-65 and 68-74 to replace the specific cell name with the corresponding product by process language. Support for these amendments may be found throughout the specification, for example, at Table 1, Figure 2, and paragraphs 143, and 202-203 in the published specification. In light of the above, Applicants respectfully request that this rejection be withdrawn and reconsidered.

B. Claims 1, 3, 4, 66, 85 and 99 remain rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not reasonably provide enablement for compositions having an intended use as vaccines or comprising "vaccine tumor cells".

The Examiner states that because claim 1 and claim 85 are drawn to compositions with the intended use of "inhibiting tumor growth" or broadly to "therapeutic compositions", the claims encompass use for the prevention of cancer. The Examiner states that Applicants' arguments with respect to the definition of "vaccine" are noted, but the claims still read on the prevention of cancer claims with the intended use of preventing cancer, which is an intended use that is not enabled by the specification as explained in the previous Office Action.

The Examiner states that because the claims contain the word "vaccine", the implied intended use for the claimed compositions is that of a prophylactic cancer vaccine, in addition to other intended uses, such as that of "stimulating an immune response". The Examiner therefore concludes that the teachings of the specification are prophetic with respect to any use as a prophylactic vaccine.

Applicants traverse this rejection. As an initial matter and as discussed in the telephonic interview of August 27th, the claims were amended in the previous response submitted March 29th, 2007 to remove the word "vaccine".

In contrast to the Examiner's conclusion that the claims are not enabled by the specification for the prevention of cancer, Applicants respectfully direct the Examiner's attention to Example 6, in particular paragraphs 165-167 of the published specification, which shows the prevention of subcutaneous tumors by vaccination with α Gal $^{(+)}$ vaccines.

Applicants disclose how to make and use the compositions of the present invention as well as demonstrate that compositions can be successfully used for the prevention of tumors. Thus, claims 1, 3, 4, 66, 85 and 99 are enabled. Therefore, one of skill in the art would be able to make and use the compositions of the claimed invention without "undue experimentation." In light of the above, Applicants submit that claims 1, 3, 4, 66, 85 and 99 are fully enabling and commensurate in scope with the disclosure of the claimed invention. Therefore, Applicants request that the rejections under 35 USC §112 be withdrawn and reconsidered.

Claims Rejections Under 35 U.S.C. § 102

A. Claim 85 remains rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Link, Jr. (U.S. 5,869,035, issued February 9, 1999). Claim 85 is drawn to tumor cells that have been transformed with α(1,3)galactosyltransferase cDNA, selected for expression of αGal epitopes and attenuated by irradiation. The Examiner states that Link, Jr. '035 teaches A375 cells that have been transformed with α(1,3)galactosyltransferase cDNA and then killed by treatment with human complement (see column 15, lines 1-29). Thus, the Examiner concludes that Link, Jr. '035 teaches compositions that are the same as that claimed.

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of anticipation because the reference does not teach each and every claim element. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon* 919 F.2d 688, 16 USPQ2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991).

As amended, claim 85 recites tumor cells that have been attenuated by irradiation. Support for this amendment may be found throughout the published specification for example at paragraph 202.

In contrast, Link, Jr. '035 describes A375 cells that have been transformed with αgalactosyltransferase (GT) DNA and then killed by treatment with human serum and complement. Applicants direct the Examiner's attention to Table H in the '035 patent which shows that A375 cells expressing αGal exposed to human serum had a viability of only 2.6 and 11.1%. '035, Col. 15. This is in direct contrast with the Examiner's conclusion that the methods of killing $\alpha\text{Gal}^{(+)}$ cells by irradiation or by lysis with human serum and human/rabbit complement produces cells that have the same physical structure. The methods to inactivate or kill the cells are not equivalent since the methods result in physical and chemical differences that have relevant functional consequences in the effectiveness of the cells in the present compositions.

Inactivation of cells by irradiation occurs mainly from the process of DNA damage. A cell carrying DNA damage as a result of exposure to ionizing radiation will either undergo apoptosis or growth arrest, which can be irreversible if the DNA cannot be repaired. Immediately after irradiation, the cell membrane is not chemically modified and will fully preserve its integrity. In fact, after irradiation, most cells will show up as viable cells after staining with a vital dye such as Trypan Blue.

Conversely, killing of αGal$^{(+)}$ cells by treatment with an anti-αGal antibody in the presence of rabbit or human complement results in a completely different set of physical and chemical alterations to the cell which will affect the efficacy of the claimed composition. Binding of anti-αGal antibodies to surface αGal epitopes results in the activation of the complement cascade which chemically modifies the cellular membrane by the attachment of complement factors that culminate in the formation of the membrane attack complex. This complex displaces the membrane phospholipids, forming a large transmembrane channel that disrupts the integrity of the cell membrane of the target cell. This disruption results in cell necrosis, immediate death and destruction of the cell. Therefore, complement-killed cells stained with a vital dye such as Trypan Blue will reveal lack of cell viability and cellular integrity.

In summary, cells killed by complement-mediated lysis will have physical and chemical alterations that result in most of the αGal epitopes being blocked by anti-αGal antibodies. Second, the lysed cells will not trigger further complement activation once administered to the patient, and thus will not provoke an acute inflammatory response, which is important for the effectiveness of these compositions as antitumor immunotherapeutic agents. Third, the lack of cell integrity will reduce the likelihood that tumor associated antigens are co-phagocytosed with the opsonized membrane fragment by antigen presenting cells, thereby reducing the possibility of mounting an immune response against soluble cytoplasmic or nuclear tumor associated antigens.

Conversely, cells attenuated by irradiation will trigger complement activation after administration to a patient, will provoke the release of complement-derived anaphylotoxins and thus trigger the recruitment of antigen presenting cells to the vaccination site. Also, as irradiation preserves the cellular integrity, phagocytosis of opsonized whole cells will result in the concomitant phagocytosis of endocellular tumor associated antigens.

For these reasons, the composition of αGal$^{(+)}$ A375 –complement killed cells described in the Link ‘035 patent is distinguishable from the claimed compositions having cells attenuated by irradiation. In light of the above, Applicants respectfully request that the rejection be reconsidered and withdrawn .

Claims Rejections Under 35 U.S.C. § 103

A. Claims 1-3, 67 and 85 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Galili, J. of Hematotherapy & Stem Cell Research 10:501-511, 2001 (cited in IDS) in view of Link, Jr., U.S. 7,005,126, issued February 28, 2006, effective filing date June 8, 1999 or Yoshimura, Cancer Letters, 164:155-160, 2001, March (cited in IDS).

The Examiner states that Galili teaches a composition of leukemia or lymphoma cells that express the α(1,3) gal epitope because the cells have been incubated in the presence of recombinant α(1,3) galactosyltransferase in solution and also neuraminidase (see abstract and page 504-505), the use of the cells as a vaccine and the cells are irradiated (see page 506 and page 508, 2nd column). The Examiner notes that Galili fails to teach leukemia or lymphoma cells that have been transformed with α(1,3)galactosyltransferase encoding cDNA, or a specific type of cancer cell.

The Examiner states that Link, Jr. '126 teaches a method of transforming human A375 melanoma cells with murine α(1,3)galactosyltransferase cDNA as well as ovarian and colon carcinoma cells, and teaches that such cells express α-gal (see column 18, line 7 - column 19, line 4), and that in athymic nude mice, transformed cells that have been exposed to human serum ex vivo do not form tumors. Yoshimura teaches the transformation of human MIA PaCa-2 human pancreatic cell line, and the huH7, human hepatocellular cell line with bovine α1-3 galactosyltransferase cDNA. The transformed cells produce the α(1,3) gal epitope, and are lysed by human antibodies and complement present in serum (see abstract, and page 156, 2nd column). The Examiner concludes it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Galili and those of either Link, Jr. or Yoshimura to make tumor cell vaccines that comprise attenuated tumor cells transformed with nucleic acid encoding α(1,3) galactosyltransferase for the purpose of creating cells that express the α(1,3) gal epitope. The Examiner writes that one would have been motivated to use Link, Jr.'s or Yoshimura's method because Link, Jr. demonstrates that using the method of transforming human tumor cells creates cells that express the α(1,3) gal epitope, and Yoshimura demonstrates the same method in other types of human cancer cells.

The Examiner states that the difference between Galili and the claimed invention is that Galili's cells which express the α (1,3) gal epitope do not contain a vector comprising α (1,3) galactosyltransferase cDNA because the α (1,3) gal epitope is created by a different method and that Galili, Link ('126 patent), and Yoshimura taught the desirability of creating an (1,3) gal epitope and one would have been motivated to have combined the references to make the claimed invention.

1. **Combining Galili with Yoshimura or the '126 patent would destroy the stated purpose of Galili.**

Applicants respectfully submit that the Office Action did not make out a *prima facie* case of obviousness because combining Galili with the '126 patent or Yoshimura reference to include cells lysed by anti-αGal antibodies and complement would destroy the stated purpose of Galili in treating lymphomas or leukemias using a composition of autologous tumor cells processed to express αGal epitopes. If a proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01.

As amended, claims 1, 2, 67 and 85 recite a mixture of human tumor cells from human tumor cell lines genetically modified to express αGal epitopes, that have been attenuated by irradiation. Support for this amendment may be found throughout the published specification for example at paragraph 202. Applicants at paragraph 109 in the published specification teach the composition of a mixture of attenuated human cells that display antigens with multiple allelic differences (reflected in differences in individual amino acids in different proteins) that provides a whole repertoire of unique allelic variants of tumor associated antigens (TAA) without the need to isolate or characterize a patient's antigens. In contrast, with respect to the cells in Galili's composition, Galili states, "[t]he only two molecular differences between the original tumor cells and the vaccinating cells are the absence of sialic acid and the de novo expression of α-gal epitopes on the latter cells." Galili, at page 508. Galili's compositions provide the same repertoire of TAAs as the one present in the patient. Conversely, Applicants' composition having human cells derived from one or more human tumor cell lines that display a repertoire of TAA with allelic differences with respect to any recipient increases the probability of breaking the pre-existing state of immunotolerance. Moreover, a mixture of one or more tumor cell lines increases the probability of having a match between the unique allelic variants of TAAs present in the vaccine compositions and the patient's self tumor associated antigens (TAAs). Importantly, the composition comprising human tumor cell lines provides more diverse "new" antigens compared to the composition in Galili to break the tolerance of the immune system to the patient's self tumor associated antigens -- which can result in effective antitumor immunity.

In contrast, Galili teaches the use of primary tumor cells freshly isolated from a patient with lymphoma that are modified in vitro with α galactosyltransferase and neuraminidase, irradiated and administered back to the donor patient. The cells in Galili provide another source of the patient's own specific tumor-associated antigens as vaccines for leukemia and lymphoma for the targeting of the vaccinating tumor cells to APC's. Galili, at page 508. Link, herein after the '126 patent, and Yoshimura teach the composition of a single in vitro cell line transformed with α galactosyltransferase. In both the '126 patent and Yoshimura, the tumor cell line expressing α galactosyltransferase is lysed with complement. '126, Column 18, line 7 - column 19, line 4, Table 3. Yoshimura, Abstract, at page 155. The '126 patent describes data from the '035 patent cited in the above section 102 rejection demonstrating that A375 cells that have been transformed with α(1,3)galactosyltransferase cDNA and then killed by treatment with human complement are not viable. Applicants direct the Examiner's attention to Table 3 in the '126 patent which shows that A375 cells expressing αGal exposed to human serum had a viability of only 2.6 and 11.1%. '126, Col. 18. Yoshimura merely repeats with the Mia-PaCa and HuH7 cell lines the work described by Link in the '035 patent. Although Yoshimura describes a composition where established tumor cell lines were genetically modified to express a bovine αgalactosyltransferase, these cells are subsequently destroyed by treatment with human serum and complement, so the final composition is not suitable to be used as an antitumor vaccine. Yoshimura, Fig 2D and 3D. As previously discussed above, cells killed by lysis and complement rather than irradiation have different physical structure, chemical composition and efficacy as vaccines.

Briefly, with respect to complement-lysed tumor cells, most of the αGal epitopes will be blocked by anti-αGal antibodies. The lysed cells will not trigger further complement activation once administered to the patient, and thus will not provoke an acute inflammatory response. Lastly, the lack of cell integrity will reduce the likelihood that tumor associated antigens are co-phagocytosed with the opsonized membrane fragment by antigen presenting cells, thus reducing the possibility of mounting an immune response against soluble cytoplasmic or nuclear tumor associated antigens.

Thus, one skilled in the art trying to tailor a vaccine composition to a patient's specific tumor associated antigens would not be motivated to combine the reference of Galili with the '126 patent or Yoshimura, since the cells of Yoshimura or the '126 patent are lysed (killed) by complement, conferring upon the cells physical and chemical differences that affect the efficacy of this composition making them unsuitable to inhibit or prevent the growth of the lymphoma cells. Therefore, since combining Galili with Yoshimura or the '126 patent would change the principle of operation of the composition being modified, one skilled in the art would not combine Galili with Yoshimura or the '126 patent. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01.

Even assuming *arguendo* that one skilled in the art would combine Galili with the '126 patent or Yoshimura, the references actually teach away from the combination because the references when combined would produce a seemingly inoperative device. *In re Sponnoble*, 405 F.2d 578, 587; 160 USPQ 237, 244 (CCPA 1969)." MPEP §2143.01. As such, one of ordinary skill in the art would not be motivated to combine these references to arrive at the Applicants' invention.

Therefore, none of the references teach or suggest a composition comprising a mixture of attenuated human cells from one or more human tumor cell lines that are attenuated by irradiation. Thus, claims 1-3, 67 and 85 are not obvious for at least the reasons argued above. Therefore, Applicants respectfully request that the rejection under 35 USC § 103 be withdrawn and reconsidered.

2. Galili and the '126 patent teach away from Applicants' claimed invention

Furthermore, Applicants respectfully submit that the Office Action did not make out a *prima facie* case of obviousness because the cited references teach away from Applicants' claimed invention. As stated above, Galili describes a vaccine composition of primary autologous tumor cells, not immortalized cell lines, to achieve a patient tailored tumor associated antigen vaccine. Galili suggests that using autologous primary tumor cells as the source of TAAs (as opposed to established tumor cell lines) would be advantageous: "Because many human TAA molecules that may serve as vaccines on various tumors have not been identified as yet, and since the combination of TAA varies in different tumors of the same type, autologous tumor cells have been viewed as potentially one of the best sources for vaccine directed against metastasizing tumors". Galili, at page 502, 2nd paragraph. Also, Galili states that "because the vaccinating tumor cells originate from the same cancer patient that undergoes vaccination, there are no unknown pathogens that may be introduced by the vaccine". Galili, at page 508, 2nd column, 2nd paragraph.

Yoshimura and the '126 patent describe complement-lysed αGal$^{(+)}$ cell lines. The '126 patent also describes a composition for treating solid tumors comprising an effective amount of xenogeneic (murine) retroviral vector producer cells having αGal epitopes in an amount that activates a hyperacute rejection response against the xenogeneic cells and an innocent bystander immune response against tumor cells. Importantly, the retroviral vector producer cell having αGal epitopes is not a source of tumor associated antigens, rather the murine $\alpha Gal^{(+)}$ cell only acts as an inflammatory agent when injected in the vicinity of a solid tumor. Lymphomas and leukemias are not solid tumors. Thus, one skilled in the art trying to tailor a vaccine composition to a patient's tumor specific antigen would not be motivated to use the xenogeneic cells of the '126 patent, since these xenogeneic cells do not have tumor associated antigens and cannot be used to inhibit growth of the lymphoma cells since there are no shared tumor associated antigens between human lymphoma cells and murine retroviral vector producer cells. Lymphomas are not solid tumors amenable to treatment by injections of murine cells in the vicinity of the tumor that would elicit an inflammatory bystander effect. Moreover, it would defeat Galili's purpose of treating lymphomas without introducing unknown pathogens carried by xenogeneic cells. Galili et al, at page 508, top of the right column.

Therefore, a person of ordinary skill, upon reading the reference would be led in a direction divergent from the path the Applicants took using modified, irradiated human tumor cells lines in their composition rather than primary tumor cells as taught by Galili, xenogeneic murine cells as taught by the '126 patent, and lysed cells as taught by Yoshimura and the '126 patent. *In re Gurley*, 27 F.3d 551, 31 USPQ 2d 1130, 1131 (Fed. Cir. 1994); *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966); *In re Sponnoble*, 405 F.2d 578, 587, 160 USPQ 237, 244 (C.C.P.A. 1969); *In re Caldwell*, 319 F.2d 254, 256, 138 USPQ 243, 245 (C.C.P.A. 1963). Thus, the cited references do not render the amended claims obvious. Accordingly, claims 1-3, 67 and 85 are not obvious for at least the reasons argued above.

Therefore, Applicants respectfully request that the rejection under 35 USC § 103 be withdrawn and reconsidered.

B. Claims 1-4 and 85 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Galili in view of Link, Jr. '126 or Yoshimura, and further in view of ATCC (ATCC Cell Lines and Hybridomas, 8th edition, 1994, page 100) .

The Examiner states that one would have had a reasonable expectation of success because both Link, Jr. and Yoshimura successfully transform multiple types of cancer cells and produce cells that express α-gal epitopes. However, the combination of Galili with Link or Yoshimura fails to tech a vaccine tumor cell composition of claim 1 where the cells are derived from A549 cells. However, the Examiner states that A549 cells are known in the art and commercially available and therefore it would have been prima facie obvious to use A549 cells in the methods of Link or Yoshimura combined with the methods of Galili.

Applicants' position with respect to Galili in view of Link, Jr. '126 or Yoshimura, is the same as that presented above, namely that combining Galili with either the '126 patent or Yoshimura would render the composition in Galili unsatisfactory for its intended purpose and therefore, there is no motivation to combine the cited references.

The addition of ATCC fails to supply the teachings that are clearly lacking in Galili, Yoshimura or the '126 patent. ATCC provides multiple human tumor cell lines but not suggest that they should be used in a composition for treating tumors, modified to express αGal and irradiated.

None of the references teach or suggest a composition comprising a mixture of attenuated human cells from one or more human tumor cell lines that are attenuated by irradiation. As such, one of ordinary skill in the art would not be motivated to combine these references to arrive at the Applicants' invention. In light of the arguments above, Applicants submit that claims 1-4, 66 and 85 are patentable and not obvious over Galili, the '126 patent or Yoshimura or ATCC. Applicants respectfully request that this rejection be reconsidered and withdrawn.

C. Claims 1 and 66 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Galili in view of Link, Jr. '126 or Yoshimura, and further in view of Berd (U.S. 6,333,028).

The Examiner states that one would have had a reasonable expectation of success because both Link, Jr. and Yoshimura successfully transform multiple types of cancer cells and produce cells that express α-gal epitopes because the use of adjuvants for tumor cell-based vaccines is known in the art and because adjuvants are known in the art to increase an immune response to components of vaccine compositions.

Applicants' position with respect to Galili in view of Link, Jr. '126 or Yoshimura, is the same as that presented above, namely that combining Galili with either the '126 patent or Yoshimura would render the composition in Galili unsatisfactory for its intended purpose and therefore, there is no motivation to combine the cited references.

The addition of Berd fails to supply the teachings that are clearly lacking in Galili, Yoshimura or the '126 patent. Berd describes the administration a composition prepared from a tumor cell which is hapten modified and syngeneic to the type of tumor to be treated in combination with an adjuvant.

None of the references teach or suggest a composition comprising a mixture of attenuated human tumor cells from one or more human tumor cell lines that are attenuated by irradiation.

As such, one of ordinary skill in the art would not be motivated to combine these references to arrive at the Applicants' invention. In light of the arguments above, Applicants submit that claims 1 and 66 are patentable and not obvious over Galili, the '126 patent or Yoshimura, or Berd. Applicants respectfully request that this rejection be reconsidered and withdrawn.

Double Patenting

Claims 1-5, 66, 67 and 85 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/013,685.

Applicants would be pleased to submit a terminal disclaimer upon notice that the pending claims are allowable.

New Grounds of Rejections

Claim 99 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiner states that claim 99 is indefinite because "the patient" lacks antecedent basis.

While not acquiescing to the Examiner's rejection, the language "the patient" has been removed from the claim rendering this rejection moot.

Conclusion

In the event that there are any questions relating to this amendment, Applicants invite the Examiner to call the undersigned attorney so that prosecution can be expedited.

No fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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